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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,636	04/26/2000	Richard B. Mazess	17620-9277	6232

7590 06/30/2004

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,636	MASCAX ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6,11,17,18,20-22,42,44,47 and 49-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6, 11, 17-18, 20-22, 42, 44, 47, and 49-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

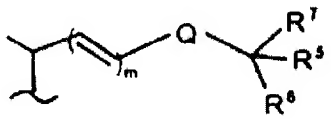
1. Claims 2-6, 11, 17-18, 20-22, 42, 44, 47, and 49-64 are pending.

2. The following new grounds of objection are necessitated by the amendment filed 4/5/04.

3. Claim 20 is objected because "comintations thereof" should have been "a combination thereof".

4. Claim 42 is objected to "combinations thereof" should have been "a combination thereof".

5. Claim 44 is objected to because (1) **R8** is not represented by formula (IIIA) and should have been represented by formula IIIB and (2) "combinations thereof" should have been "a combination thereof".



(IIIA)

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wherein m is R^8 or 1; R^5 is H OH; R^6 or R^7 are independently H, OH, lower alkyl, lower fluoroalkyl, *O*-lower alkyl, *O*-lower acyl, *O*-aromatic alkyl, lower cycloalkyl or, taken together

6. Claim 49 is objected to because "combinations thereof" should be "a combination thereof".

7. Claim 50 is objected to because "a" is missing before "combination thereof".

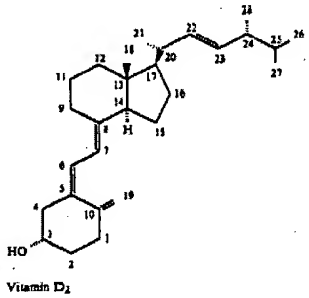
8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

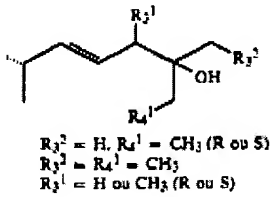
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 2-6, 20, 44, 47, 49-51, 53-56, 58-62 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,232,836 (of record, August 1993, PTO 892).

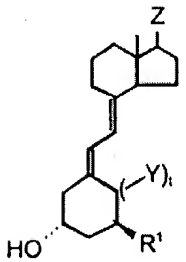
The '836 patent teaches a conjugate comprising at least one vitamin D moiety having the formula (See col. 1, in particular)



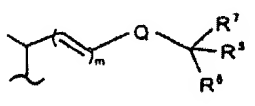
having the side chain



(See col. 7, in particular) that is identical to the formula shown in instant claim 20



where R1 is H, Y is CH2, t is 1, Z is a side chain having the formula

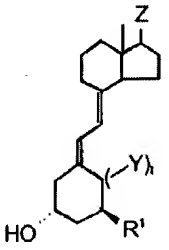


where m is 0, Q is

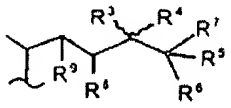
where n is 1, R3 is CH3, R4 is H, R5 is OH, R6 is alkyl and R7 is alkyl.

The reference further teaches the vitamin D moiety having the side chain

The reference conjugate mentioned above is also identical to the formula as shown in instant claims 44 and 49 where the vitamin D moiety is



where R1 is H, Y is CH2, t is 1, Z is a side chain having the formula



where R9 is H, R8 is H taken together to form a double bond between C-22 and C-23, R3 is CH3, R4 is H and R5 is OH, R6 and R7 are alkyl.

The reference vitamin D moiety is associated with (conjugated to) phosphate or bisphosphate (See claim 1 of '836 patent, col. 53, line 16-17, in particular) which inherently targets to bone The '836 patent further teaches various vitamin D conjugate such as vitamin D conjugate to proteins, polypeptides, glycoproteins (column 27, line 11-68, column 28, in particular), antibody (column 28 lines 38, in particular), enzyme or radioisotope (See column 28, lines 35-41, in particular). The '836 patent further teaches a pharmaceutical composition comprising the reference conjugate (See column 45-46, in particular). The '836 patent teaches that the conjugate can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular). The reference vitamin D moiety is linked directly via chemical bond or indirectly through a functional group such as amine, lysine, thiol group of cysteine or N-hydroxysuccinimide (See col. 27, lines 26-41, in particular). The reference conjugate is useful treatment of osteoporosis (col. 3, line 53, in particular). Thus, the reference teachings anticipate the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 3, 5, 11, 17-18, 20, 44, 49-54, 57, and 59-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,232,836 (of record, August 1993, PTO 892) in view of Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme *et al* (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 (of record, December 1992, PTO 892).

The teachings of the '836 patent have been discussed supra. The '836 patent further, teaches that any compound can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular).

The claimed invention in claims 18, 20, 44, 49, 54, 59 and 60 differs from the teachings of the reference only that the conjugate wherein the targeting molecule is bisphosphonate or calcitonin.

The claimed invention in claim 11 differs from the teachings of the reference only in that the conjugate wherein the bifunctional connector is an amino acid chelated to the target molecule moiety and linked to the vitamin D moiety via an amide linkage.

The claimed invention in claim 17 differs from the teachings of the reference only in that the conjugate further comprises at least one therapeutic agent other than vitamin D moiety conjugated therewith.

Bauss *et al* teach a method of conjugating bone seeking agent such as bisphosphonate and tetracycline with bone preserving agent such as estrogen and other steroids (E2-BPs) (See page 168, column 2, Materials and Methods, Figure 1, in particular). Bauss *et al* teach that estradiol-bisphosphonates conjugates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular).

Orme *et al* teach a conjugate such as β-estradiol-3-benzoate-17-succinyl-12A-Tetracycline that targets to the tissue of interest such as bone (See page 1375, in particular). The reference steroid moiety such as β-estradiol-3-benzoate is associated with a target moiety such as Tetracycline having an affinity for a tissue of interest such as bone, which is not plasma (See Title, abstract, page 1375, in particular). The reference steroid moiety is associated with the target molecule moiety via a connecting group such as succinate ester which is a bifunctional connector that forms a bond between said steroid moiety and said target molecule moiety (See page 1376, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular).

The WO 92/21355 publication teaches a method for building of bone in a human subject suffering from age-related bone loss comprising administering to a subject a supplement comprising calcitonin which decreases the rates of bone resorption in osteoporotic patients (See page 11, line 29-30, in particular), Vitamin D such as cholecalciferol (D3), ergocalciferol (D2) and its biologically active metabolites and precursors such as 1α, 25 OH(2) vitamin D, where the vitamin D promotes intestinal absorption of calcium, and contributing to plasma calcium regulation by acting on bone density and stimulate reabsorption of calcium by the kidney while diphosphonates (also known as Didronel, disodium salt of 1-hydroxyethylidene diphosphonic acid EHDP or editronate) which act primarily on the bone (See page 12, Didronel, claims 1, and 4

of WO 92/21355 publication, in particular). The WO 92/21355 publication teaches that bisphosphonates inhibit the formation, growth and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surface (See page 12, lines 14-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the phosphate or bisphosphate as taught by the '836 patent for the bisphosphonate as taught by Bauss *et al* and the WO 92/21355 publication or the calcitonin as taught by the WO 92/21355 publication or the tetracycline as taught by Orme *et al* in a conjugate comprising a vitamin D moiety associated with bisphosphate or calcitonin or tetracycline via a linking group as taught by the '836 patent, Bauss *et al,* Orme *et al* and the WO 92/21355 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 92/21355 publication teaches that Vitamin D promotes intestinal absorption of calcium, and contributing to plasma calcium regulation by acting on bone density and stimulate reabsorption of calcium by the kidney; diphosphonates (also known as Didronel, disodium slat of 1-hydroxyethylidene diphosphonic acid EHDP or editronate) act primarily on the bone (See page 12, Didronel, claims 1, and 4 of WO 92/21355 publication, in particular) while bisphosphonates inhibit the formation, growth and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surface (See page 12, lines 14-16, in particular).

The '836 patent teaches that any compound can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular). Bauss *et al* teach that estradiol-bisphosphonates conjugates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting

systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). Claim 2 is included in this rejection because the vitamin D moiety is conjugated to the target molecule moiety, which is 1:1 ratio. Claim 11 is included in this rejection because N-hydroxy-succinimidyl ester is a good reagent for reaction with Lysine, which is an amino acid that forms an amide linkage through α-amino group or the ε aliphatic amino group. In addition, the N-hydroxy-succinimidyl ester reacts with the carboxyl group or thiol group of Cysteine amino acid residue that can be chelated. Claim 17 is included in this rejection because additional therapeutic agent such as estrogen which is other than vitamin D moiety can be conjugated therewith as taught by Bauss *et al* and Orme *et al* since estrogen therapy has been used for the treatment of osteoporosis, disease related to bone.

8. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,232,836 (August 1993, PTO 892) in view of Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme *et al* (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 publication (December 1992, PTO 892) as applied to claims 3, 5, 11, 17-18, 20, 44, 49-54, 57, and 59-64 mentioned above and further in view of US Pat No. 6,309,666 (of record, Oct 2001, PTO 892).

The combined teachings of the '836 patent, Bauss *et al*, Orme *et al* and WO 92/21355 publication have been discussed supra.

The claimed invention in claim 21 differs from the teachings of the references only that the pharmaceutical composition further comprises a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate.

The claimed invention in claim 22 differs from the teachings of the references only that the pharmaceutical composition further comprises a differentially degradable coating wherein said coating is an enteric coating.

The '666 patent teaches a pharmaceutical preparation in the form of a coated capsule or enteric coating such as gelatin polymer capsule for time release delivery of any kind of

medicament such as prednisolone (See entire document, abstract, column 6 lines 66-67 bridging column 7, lines 1-7, column 20, lines 25, in particular). The '666 patent teaches that the time period from the discharge of the pharmaceutical preparation from the stomach till the contents of the hard capsule start to be released can be controlled to any length by selecting the kind and/or amount of polymer(s) used for a low pH soluble polymer film and/or the kind of the acidic substance (See column 3, lines 31-38, in particular). The reference pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the prednisolone in the polymer capsule for time release delivery as taught by the '666 patent for the a conjugate comprising at least one vitamin D moiety being associated with a targeting moiety such as bisphosphonate, phosphate, tetracycline or calcitonin having an affinity for bone as taught by the '836 patent, Bauss *et al,* Orme *et al* and the WO 92/21355 publication From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '666 patent teaches that the enteric coating pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular).

10. Claim 42 would be allowed once the correction as indicated above is made.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

6. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 28, 2004

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